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*** YOU HAVE NEW MAIL ***

=> s alpha 2B and alpha 2C and adrenergic
L1          456 ALPHA 2B AND ALPHA 2C AND ADRENERGIC

=> s l1 and therapeut?
L2           72 L1 AND THERAPEUT?

=> s l2 and recpetor subtype?
L3            0 L2 AND RECPETOR SUBTYPE?

=> s l2 and adrenergic receptor subtype
L4           32 L2 AND ADRENERGIC RECEPTOR SUBTYPE

=> s l4 and bind?(2a) alpha 2B
L5            2 L4 AND BIND?(2A) ALPHA 2B

=> d l5 bib abs 1-2

L5   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2002 ACS
AN   2002:521523  CAPLUS
DN   137:73273
TI   Adrenergic receptor ligand-neurotoxin conjugates and methods for
     treating pain
IN   Gil, Daniel W.; Aoki, Kei Roger
PA   Allergan Sales, Inc., USA
SO   PCT Int. Appl., 76 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
PI   WO 2002053177      A2    20020711       WO 2001-US48651  20011214
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,
             VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI US 2000-751053 A 20001229
OS MARPAT 137:73273
AB Agents for treating pain, methods for producing the agents, and methods for treating pain by administration to a patient of a **therapeutically** effective amt. of the agent, are disclosed. The agent may include a clostridial neurotoxin, a fragment or a deriv. thereof, attached to a targeting component, wherein the targeting component is selected form a group consisting of compds. which selectively **binds** at the .**alpha**.**2b** or .**alpha**.**2b**/.**alpha**.**2c adrenergic receptor subtype**(s) as compared to other binding sites, e.g. the .alpha.2a **adrenergic receptor subtype**
.

L5 ANSWER 2 OF 2 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-619081 [66] WPIDS
DNC C2002-174840
TI Agent for treating pain such as neuropathic pain comprises a **therapeutic** component and a targeting component.
DC B04 B05
IN AOKI, K R; GIL, D W
PA (ALLR) ALLERGAN SALES INC
CYC 96
PI WO 2002053177 A2 20020711 (200266)* EN 76p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
ADT WO 2002053177 A2 WO 2001-US48651 20011214
PRAI US 2000-751053 20001229
AN 2002-619081 [66] WPIDS
AB WO 200253177 A UPAB: 20021014
NOVELTY - An agent comprises a **therapeutic** component (a) and a targeting component (b), where the targeting component selectively **binds** at the **alpha** -**2B**/ alpha -C **adrenergic receptor subtype** as compare to the alpha -2A **adrenergic receptor subtype**.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for making the agent involving producing a polypeptide from a gene having codes for at least one component of the agent.
ACTIVITY - Analgesic; Cytostatic; Antiinflammatory.
MECHANISM OF ACTION - **alpha** -**2B** **adrenergic** receptor **binder**; **Alpha**-**2B**/**alpha**-**2C adrenergic** receptor binder.
USE - The novel **therapeutic** agent is used for treating pain such as chronic pain, visceral pain, neuropathic pain, referred pain and allodynia type pain (persisting from 2 - 27 months) without affecting acute pain sensation or tactile sensation such as chronic pain, visceral pain, neuropathic pain, referred pain and allodynia type pain (claimed) and for treating pain associated with cancer and irritable bowel syndrome.
ADVANTAGE - (b) selectively **binds** at the **alpha** -**2B** or **alpha** -**2B**/ **alpha** 2B-**alpha** -**2C adrenergic** receptor subtypes(s) as compared to the alpha -2A **adrenergic receptor subtype**. (a) inactivates cellular ribosomes.
Dwg.0/1

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FILE 'BIOSIS, MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 13:50:03 ON 22 NOV 2002

L1 456 S ALPHA 2B AND ALPHA 2C AND ADRENERGIC
L2 72 S L1 AND THERAPEUT?
L3 0 S L2 AND RECPETOR SUBTYPE?
L4 32 S L2 AND ADRENERGIC RECEPTOR SUBTYPE
L5 2 S L4 AND BIND?(2A) ALPHA 2B

=> s l1 and ADRENERGIC RECEPTOR SUBTYPE
L6 84 L1 AND ADRENERGIC RECEPTOR SUBTYPE

=> s l6 and BIND?(2A) ALPHA 2B
L7 2 L6 AND BIND?(2A) ALPHA 2B

=> s target? (2a) ligand (3a) bind? (3a) alpha 2B
L8 0 TARGET? (2A) LIGAND (3A) BIND? (3A) ALPHA 2B

=> s alpha 2B adrenergic receptor subtype?
L9 24 ALPHA 2B ADRENERGIC RECEPTOR SUBTYPE?

=> s l9 and Bind?
L10 17 L9 AND BIND?

=> s l10 and therapeut?
L11 0 L10 AND THERAPEUT?

=> s l10 and agent
L12 1 L10 AND AGENT

=> d l12 bib abs

L12 ANSWER 1 OF 1 MEDLINE
AN 97461148 MEDLINE
DN 97461148 PubMed ID: 9316829
TI Mechanism of down-regulation of alpha-2 adrenergic receptor subtypes.
AU Heck D A; Bylund D B
CS Department of Pharmacology, University of Nebraska Medical Center, Omaha 68198-6260, USA.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Sep) 282 (3) 1219-27.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971105
Last Updated on STN: 20000303
Entered Medline: 19971017
AB Long-term exposure to agonist down-regulates receptor expression for many G protein-coupled receptors. This decrease in receptor density could occur through either an increase in receptor degradation or a decrease in receptor synthesis. We studied the mechanism of down-regulation of the alpha-2A and **alpha-2B adrenergic receptor subtypes** transfected into the Chinese hamster ovary cell line as well as the alpha-2A receptor endogenous to the HT29 cell line. The rate constants for receptor appearance and disappearance were calculated from the recovery of receptor expression after irreversible inactivation of the existing receptor population with an alkylating **agent**. In the presence of the agonist norepinephrine, the receptor subtypes in all three cell lines down-regulated to about 50%

with a half-time of 2.5 hr. When recovering in the presence of norepinephrine after irreversible inactivation, the rate of receptor degradation increased approximately 2-fold for all three cell lines with little change in the rate of synthesis. During this recovery, the transfected alpha-2A receptor exhibited a half-life of 3.0 hr, which agrees with the 2.7-hr half-time of down-regulation in the presence of norepinephrine. In contrast, the transfected alpha-2B receptor and the endogenous alpha-2A receptor had a half-life of 1.2 hr and 8.9 hr, respectively. For only the endogenous alpha-2A receptor, pertussis toxin increased the half-time of down-regulation to 9.8 hr, similar to the 8.9-hr receptor half-life in the presence of norepinephrine during recovery after irreversible inactivation. Our results indicate that the mechanism of down-regulation of the alpha-2A and -2B adrenergic receptor subtypes is an increase in the rate of receptor degradation.

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     FILE 'BIOSIS, MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 13:50:03 ON
     22 NOV 2002
L1           456 S ALPHA 2B AND ALPHA 2C AND ADRENERGIC
L2            72 S L1 AND THERAPEUT?
L3             0 S L2 AND RECPETOR SUBTYPE?
L4            32 S L2 AND ADRENERGIC RECEPTOR SUBTYPE
L5             2 S L4 AND BIND?(2A) ALPHA 2B
L6            84 S L1 AND ADRENERGIC RECEPTOR SUBTYPE
L7             2 S L6 AND BIND?(2A) ALPHA 2B
L8             0 S TARGET? (2A) LIGAND (3A) BIND? (3A) ALPHA 2B
L9            24 S ALPHA 2B ADRENERGIC RECEPTOR SUBTYPE?
L10           17 S L9 AND BIND?
L11            0 S L10 AND THERAPEUT?
L12            1 S L10 AND AGENT

=> s l10 and pain
L13            0 L10 AND PAIN

=> s l10 and thera?
L14            0 L10 AND THERA?

=> s l10 and treatment
L15            0 L10 AND TREATMENT

=> s l10 and imiloxan
L16            0 L10 AND IMILOXAN

=> s l1 and imiloxan
L17            8 L1 AND IMILOXAN

=> s l17 not l5
L18            7 L17 NOT L5

=> d l18 bib abs 1-7

L18  ANSWER 1 OF 7  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN   1995:270868  BIOSIS
DN   PREV199598285168
TI   Peripheral nociceptive effects of alpha-2-adrenergic receptor
     agonists in the rat.
AU   Khasar, S. G.; Green, P. G.; Chou, B.; Levine, J. D. (1)
CS   (1) Dep. Med., Div. Neurosci., Univ. California, San Francisco, CA
     94143-0452 USA
SO   Neuroscience, (1995) Vol. 66, No. 2, pp. 427-432.
```

ISSN: 0306-4522.
DT Article
LA English
AB We have previously shown that norepinephrine can produce hyperalgesia via an alpha-2-**adrenergic** receptor mechanism. The alpha-2-**adrenergic** receptor agonist clonidine has, however, also been shown to produce peripheral analgesia. In view of the multiple alpha-2-subtypes currently known (i.e. alpha-2A, **alpha-2B** and **alpha-2C**), we evaluated the alpha-2-receptor subtypes mediating norepinephrine-induced peripheral hyperalgesia and clonidine analgesia. Norepinephrine and the alpha-2-**adrenergic** agonists clonidine and UK 14,304 (1-1000 ng), when co-injected with the calcium ionophore A23187 (1000 ng) produced dose-dependent hyperalgesia in the Randall-Selitto paw withdrawal test. Norepinephrine (100 ng) hyperalgesia was dose-dependently antagonized by alpha-2-**adrenergic** receptor antagonists. From the estimated ID-50, the rank order of potency was: SK&F 104856 (**alpha-2B**) simeq **imiloxan** (**alpha-2B**) gt rauwolscine (**alpha-2C**) mchgt BRL 44408 (alpha-2A). Norepinephrine hyperalgesia was not significantly affected by pertussis-toxin treatment. Prostaglandin E-2 (100 ng) hyperalgesia was inhibited dose-dependently, by clonidine and UK 14,304. Rauwolscine was more potent in reversing the inhibitory effect of clonidine on prostaglandin E-2 than **imiloxan** while BRL 44408 was ineffective. The inhibitory effect of clonidine on prostaglandin E-2 hyperalgesia was reversed by pertussis toxin. These data suggest that **alpha-2B**-subtype receptors mediate (norepinephrine hyperalgesia while the antinociceptive effect of alpha-2-agonist is mediated by the **alpha-2C**-subtype receptor. Differential coupling of these receptor subtypes to second messenger systems and location on different cell types in the rat paw may explain, at least in part, their differential responses to alpha-2-agonist stimulation, leading to hyperalgesia and analgesia.

L18 ANSWER 2 OF 7 MEDLINE
AN 2001409271 MEDLINE
DN 21149786 PubMed ID: 11250880
TI The role of several alpha(1)- and alpha(2)-adrenoceptor subtypes mediating vasoconstriction in the canine external carotid circulation.
AU Willems E W; Valdivia L F; Saxena P R; Villalon C M
CS Department of Pharmacology, Erasmus University Medical Centre Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.
SO BRITISH JOURNAL OF PHARMACOLOGY, (2001 Mar) 132 (6) 1292-8.
Journal code: 7502536. ISSN: 0007-1188.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200107
ED Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719
AB 1. It has recently been shown that both alpha(1)- and alpha(2)-adrenoceptors mediate vasoconstriction in the canine external carotid circulation. The present study set out to identify the specific subtypes (alpha(1A), alpha(1B) and alpha(1D) as well as alpha(2A), **alpha(2B)** and **alpha(2C)**) mediating the above response. 2. Consecutive 1 min intracarotid infusions of phenylephrine (alpha(1)-adrenoceptor agonist) and BHT933 (alpha(2)-adrenoceptor agonist) produced dose-dependent decreases in external carotid blood flow, without affecting mean arterial blood pressure or heart rate. 3. The responses to phenylephrine were selectively antagonized by the antagonists, 5-methylurapidil (alpha(1A)) or BMY7378 (alpha(1D)), but not by L-765,314 (alpha(1B)), BRL44408 (alpha(2A)), **imiloxan** (**alpha(**

2B)) or MK912 (**alpha(2C)**). In contrast, only BRL44408 or MK912 affected the responses to BHT933. 4. The above results support our contention that mainly the alpha(1A), alpha(1D), alpha(2A) and **alpha(2C)**-adrenoceptor subtypes mediate vasoconstriction in the canine external carotid circulation.

L18 ANSWER 3 OF 7 MEDLINE
AN 96078081 MEDLINE
DN 96078081 PubMed ID: 7477883
TI Peripheral nociceptive effects of alpha 2-**adrenergic** receptor agonists in the rat.
AU Khasar S G; Green P G; Chou B; Levine J D
CS Department of Medicine, University of California, San Francisco 94143-0452, USA.
NC NS23647 (NINDS)
SO NEUROSCIENCE, (1995 May) 66 (2) 427-32.
Journal code: 7605074. ISSN: 0306-4522.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951207
AB We have previously shown that norepinephrine can produce hyperalgesia via an alpha 2-**adrenergic** receptor mechanism. The alpha 2-**adrenergic** receptor agonist clonidine has, however, also been shown to produce peripheral analgesia. In view of the multiple alpha 2-subtypes currently known (i.e. alpha 2A, **alpha 2B** and **alpha 2C**), we evaluate the alpha 2-receptor subtypes mediating norepinephrine-induced peripheral hyperalgesia and clonidine analgesia. Norepinephrine and the alpha 2-**adrenergic** agonists clonidine and UK 14,304 (1-1000 ng), when co-injected with the calcium ionophore A23187 (1000 ng) produced dose-dependent hyperalgesia in the Randall-Selitto paw withdrawal test. Norepinephrine (100 ng) hyperalgesia was dose-dependently antagonized by alpha 2-**adrenergic** receptor antagonists. From the estimated ID50, the rank order of potency was: SK&F 104856 (**alpha 2B**) approximately **imiloxan** (**alpha 2B**) > rauwolscine (**alpha 2C**) >> BRL 44408 (alpha 2A). Norepinephrine hyperalgesia was not significantly affected by pertussis-toxin treatment. Prostaglandin E2 (100 ng) hyperalgesia was inhibited dose-dependently, by clonidine and UK 14,304. Rauwolscine was more potent in reversing the inhibitory effect of clonidine on prostaglandin E2 than **imiloxan** while BRL 44408 was ineffective. The inhibitory effect of clonidine on prostaglandin E2 hyperalgesia was reversed by pertussis toxin. These data suggest that **alpha 2B**-subtype receptors mediate (norepinephrine hyperalgesia while the antinociceptive effect of alpha 2-agonist is mediated by the **alpha 2C**-subtype receptor. Differential coupling of these receptor subtypes to second messenger systems and location on different cell types in the rat paw may explain, at least in part, their differential responses to alpha 2-agonist stimulation, leading to hyperalgesia and analgesia.

L18 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 2001:411333 CAPLUS
DN 135:313378
TI Pharmacological profile of the mechanisms involved in the external carotid vascular effects of the antimigraine agent isometheptene in anesthetized dogs
AU Willems, Edwin W.; Valdivia, Luis Felipe; Saxena, Pramod R.; Villalon, Carlos M.

CS Department of Pharmacology, Erasmus University Medical Centre Rotterdam "EMCR", Rotterdam, 3000 DR, Neth.
SO Naunyn-Schmiedeberg's Archives of Pharmacology (2001), 364(1), 27-32
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer-Verlag
DT Journal
LA English
AB This work investigated the external carotid vascular effects of isometheptene in vagosympathectomized dogs, anesthetized with pentobarbital. One-minute intracarotid infusions of isometheptene (10, 30, 100 and 300 .mu.g/min) produced dose-dependent decreases in external carotid blood flow, without affecting blood pressure or heart rate. The vasoconstrictor responses to 100 and 300 .mu.g isometheptene/min were clearly attenuated in animals pretreated with reserpine (5000 .mu.g/kg). Moreover, after prazosin (an .alpha.1-adrenoceptor antagonist; 100 .mu.g/kg), the responses to isometheptene remained unaltered in reserpine-untreated as well as reserpine-pretreated dogs. In contrast, the responses to isometheptene were attenuated by rauwolscine (an .alpha.2-adrenoceptor antagonist; 300 .mu.g/kg) in reserpine-untreated animals and were practically abolished in reserpine-pretreated dogs. Further investigation into the specific .alpha.2-adrenoceptor subtypes, using selective antagonists, showed that BRL44408 (.alpha.2A) and MK912 (. **alpha.2C**) markedly attenuated this response, while **imiloxan** (.**alpha.2B**) was ineffective. The involvement of 5-HT1B and 5-HT1D receptors seems highly unlikely, since antagonists at 5-HT1B (SB224289) and 5-HT1D (BRL15572) receptors (both at 300 .mu.g/kg) were ineffective. It is concluded that isometheptene-induced canine external carotid vasoconstriction is mediated by both indirect (a tyramine-like action) and direct (acting at receptors) mechanisms, which mainly involve .alpha.2A- and .**alpha.** **2C**-adrenoceptors, while the involvement of .alpha.1-adrenoceptors seems rather limited.
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1998:230070 CAPLUS
DN 129:561
TI Ligand efficacy and potency at recombinant .alpha.2 **adrenergic** receptors. Agonist-mediated [35S]GTP.gamma.S binding
AU Jasper, Jeffrey R.; Lesnick, John D.; Chang, L. Katy; Yamanishi, Susan S.; Chang, Thomas K.; Hsu, Sherry A. O.; Daunt, David A.; Bonhaus, Douglas W.; Eglen, Richard M.
CS Center for Biological Research, Neurobiology Unit, Roche Bioscience, Palo Alto, CA, 94304, USA
SO Biochemical Pharmacology (1998), 55(7), 1035-1043 Adonis
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB Alpha-2 **adrenergic** receptors (.alpha.2 AR) mediate incorporation of guanosine 5'-O-(.gamma.-thio)triphosphate ([35S]GTP.gamma.S) into isolated membranes via receptor-catalyzed exchange of [35S]GTP.gamma.S for GDP. In the current study, we used [35S]GTP.gamma.S incorporation to characterize the intrinsic activity and potency of agonists and antagonists at the cloned mouse .alpha.2a/d and human .alpha.2a, . **alpha.2b** ARs. Full agonists increased [35S]GTP.gamma.S binding to membranes by 2- to 3-fold. Antagonists did not increase [35S]GTP.gamma.S binding but competitively inhibited agonist-stimulated [35S]GTP.gamma.S binding. Compds. with intrinsic activities less than that of the full agonists norepinephrine (NE) or epinephrine (EPI) were capable of antagonizing agonist-stimulated [35S]GTP.gamma.S binding. The agonistic properties of a no. of .alpha.2 AR ligands were characterized at each .alpha.2 AR subtype. The rank order of agonist potency for selected

compds. at the human receptors (with intrinsic activity compared with NE, defined as 1.0) was: .alpha.2a: Dexmedetomidine (0.73) > guanabenz (0.38) > UK-14304 (1.02) > clonidine (0.32) > ST-91 (0.63) > NE (1.00). . **alpha.2b**: Dexmedetomidine (1.10) > clonidine (0.18) > guanabenz (0.71) > NE (1.00) ST-91 (0.44) > UK-14304 (0.59). . **alpha.2c**: Dexmedetomidine (1.03) > NE (1.00) > UK-14304 (0.75) > ST-91 (0.32) .gtoreq. clonidine (0.23) .mchgt. guanabenz (0). This report provides a functional characterization of **adrenergic** receptor ligands at human and mouse .alpha.2a/d AR. It also illustrates the utility of [35S]GTP.gamma.S incorporation as a function marker of receptor activation.

L18 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1995:560390 CAPLUS
DN 123:797
TI Peripheral nociceptive effects of .alpha.2-**adrenergic** receptor agonists in the rat
AU Khasar, S. G.; Green, P. G.; Chou, B.; Levine, J. D.
CS Deps. Med., Anatomy, Oral, Maxillofacial Surgery, Univ. California, San Francisco, CA, 94143-0452, USA
SO Neuroscience (Oxford) (1995), 66(2), 427-32
CODEN: NRSCDN; ISSN: 0306-4522
PB Elsevier
DT Journal
LA English
AB It was previously shown that norepinephrine can produce hyperalgesia via an .alpha.2-**adrenergic** receptor mechanism. The .alpha.2-**adrenergic** receptor agonist clonidine has, however, also been shown to produce peripheral analgesia. In view of the multiple .alpha.2-subtypes currently known (i.e. .alpha.2A, .**alpha**.**2B** and .**alpha**.**2C**), the .alpha.2-receptor subtypes mediating norepinephrine-induced peripheral hyperalgesia and clonidine analgesia were investigated. Norepinephrine and the .alpha.2-**adrenergic** agonists clonidine and UK 14,304 (1-1000 ng), when co-injected into rats with the Ca ionophore A23187 (1000 ng) produced dose-dependent hyperalgesia in the Randall-Selitto paw withdrawal test. Norepinephrine (100 ng)-induced hyperalgesia was dose-dependently antagonized by .alpha.2-**adrenergic** receptor antagonists. From the estd. ID50 values, the rank order of potency was: SKF 104856 (.**alpha**.**2B**) .simeq. **imiloxan** (.**alpha**.**2B**) > rauwolscine (.**alpha**.**2C**) .mchgt. BRL 44408 (.alpha.2A). Norepinephrine-induced hyperalgesia was not affected by pertussis-toxin treatment. PGE2 (100 ng)-induced hyperalgesia was inhibited dose-dependently by clonidine and UK 14,304. Rauwolscine was more potent in reversing the inhibitory effect of clonidine on PGE2 than was **imiloxan**, while BRL 44408 was ineffective. The inhibitory effect of clonidine on PGE2-induced hyperalgesia was reversed by pertussis toxin. These data suggest that .**alpha**.**2B**-subtype receptors mediate norepinephrine hyperalgesia, while the antinociceptive effect of .alpha.2-agonists is mediated by the .**alpha**.**2C** -subtype receptor. Differential coupling of these receptor subtypes to 2nd messenger systems and location on different cell types in the rat paw may explain, at least in part, their differential responses to .alpha.2-agonist stimulation, leading to hyperalgesia and analgesia.

L18 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1993:117293 CAPLUS
DN 118:117293
TI .alpha.2-Autoreceptor subclassification in rat isolated kidney by use of short trains of electrical stimulation
AU Bohmann, C.; Schollmeyer, P.; Rump, L. C.
CS Med. Universitaetsklin. Freiburg, Freiburg, 7800, Germany
SO British Journal of Pharmacology (1993), 108(1), 262-8
CODEN: BJPCBM; ISSN: 0007-1188

DT Journal
LA English
AB Rat kidneys were perfused with Krebs-Henseleit soln. and incubated with [3H]noradrenaline. When the renal nerves were elec. stimulated at either 1 Hz for 30 s or 100 Hz for 0.06 s, the stimulation-induced (S-I) outflow of radioactivity was taken as an index of endogenous noradrenaline release. At a frequency of 1 Hz for 30 s, the .alpha.-adrenoceptor antagonists BRL 44408 (0.01 or 0.1 .mu.M) and **imiloxan** (0.1 or 1.0 .mu.M) enhanced S-I outflow of radioactivity. However, at a frequency of 100 Hz for 0.06 s, the .alpha.-adrenoceptor antagonists, idazoxan (0.1 or 1.0 .mu.M), **imiloxan** (0.1 or 1.0 .mu.M), BRL 44408 (0.1 or 1.0 .mu.M), BRL 41992 (0.1 or 1.0 .mu.M), and prazosin (0.01 .mu.M) failed to enhance S-I outflow of radioactivity. Thus, the rat isolated kidney stimulated at 100 Hz for 0.06 s avoids autoinhibition by endogenous noradrenaline, and .alpha.-adrenoceptor antagonist affinities (pKB) at the prejunctional .alpha.-autoreceptor were estd. without disturbance by the endogenous activator. The .alpha.2-adrenoceptor agonist, clonidine, inhibited the S-I outflow of radioactivity with a max. of 90% and an EC50 of 7.2 nM. All .alpha.-adrenoceptor antagonists used caused parallel shifts of the concn.-response curve for clonidine to the right. The rank order of potencies was: rauwolscine (.alpha.2A/B) > idazoxan (.alpha.2A/B) > phentolamine (.alpha.2A/B) > WB 4101 (.alpha.2A) > BRL 44408 (.alpha.2A) > BRL 41992 (.**alpha**.**2B**) > prazosin (.**alpha**.
2B) = **imiloxan** (.**alpha**.**2B**). These
data, when compared with binding, mol., and functional data of various other tissues and cell lines, indicated that prejunctional .alpha.2-autoreceptors in rat kidney do not belong to the .**alpha**
.**2B**- or .**alpha**.**2C**-subtype. The
.alpha.2-autoreceptor of rat kidney seems to be of the .alpha.2A-subtype. However, .alpha.2-autoreceptor affinities of the present study also correlate well with binding affinities of the recently described .alpha.2D-ligand binding site in bovine pineal gland.

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=> s alpha 2b and alpha 2c and adrenergic
L20         456 ALPHA 2B AND ALPHA 2C AND ADRENERGIC

=> s l20 and saporin
L21           2 L20 AND SAPORIN

=> d l21 bib abs 1-2

L21  ANSWER 1 OF 2     MEDLINE
AN   2001124396     MEDLINE
DN   20574867   PubMed ID: 11125002
TI   Antinociceptive action of nitrous oxide is mediated by stimulation of
     noradrenergic neurons in the brainstem and activation of [alpha]
     2B adrenoceptors.
AU   Sawamura S; Kingery W S; Davies M F; Agashe G S; Clark J D; Kobilka B K;
     Hashimoto T; Maze M
CS   Department of Anesthesia, Stanford University School of Medicine,
     Stanford, California 94305, USA.
NC   GM30232 (NIGMS)
SO   JOURNAL OF NEUROSCIENCE, (2000 Dec 15) 20 (24) 9242-51.
     Journal code: 8102140. ISSN: 1529-2401.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200102
ED   Entered STN: 20010322
     Last Updated on STN: 20010521
     Entered Medline: 20010222
AB   Although nitrous oxide (N(2)O) has been used to facilitate surgery for
     >150 years, its molecular mechanism of action is not yet defined. Having
     established that N(2)O-induced release of norepinephrine mediates the
     analgesic action at alpha(2) adrenoceptors in the spinal cord, we now
     investigated whether activation of noradrenergic nuclei in the brainstem
     is responsible for this analgesic action and which alpha(2) adrenoceptor
     subtype mediates this property. In rats, Fos immunoreactivity was examined
     in brainstem noradrenergic nuclei after exposure to nitrous oxide. After
     selective lesioning of noradrenergic nuclei by intracerebroventricular
     application of the mitochondrial toxin saporin, coupled to the
     antibody directed against dopamine beta hydroxylase (DbetaH-
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saporin), the analgesic and sedative actions of N(2)O were determined. Null mice for each of the three alpha(2) adrenoceptor subtypes (alpha(2A), **alpha(2B)**, and **alpha(2C**)), and their wild-type cohorts, were tested for their antinociceptive and sedative response to N(2)O. Exposure to N(2)O increased expression of Fos immunoreactivity in each of the pontine noradrenergic nuclei (A5, locus coeruleus, and A7). DbetaH-**saporin** treatment eliminated nearly all of the catecholamine-containing neurons in the pons and blocked the analgesic but not the sedative effects of N(2)O. Null mice for the **alpha(2B)** adrenoceptor subtype exhibited a reduced or absent analgesic response to N(2)O, but their sedative response to N(2)O was intact. Our results support a pivotal role for noradrenergic pontine nuclei and **alpha(2B)** adrenoceptors in the analgesic, but not the sedative effects of N(2)O. Previously we demonstrated that the analgesic actions of alpha(2) adrenoceptor agonists are mediated by the alpha(2A) subtype; taken together with these data we propose that exogenous and endogenous alpha(2) adrenoceptor ligands activate different alpha(2) adrenoceptor subtypes to produce their analgesic action.

L21 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 2002:145484 CAPLUS
DN 137:195403
TI Isoflurane and nociception: spinal .alpha.2A adrenoceptors mediate antinociception while supraspinal .alpha.1 adrenoceptors mediate pronociception
AU Kingery, Wade S.; Agashe, Geeta S.; Guo, Tian Z.; Sawamura, Shigehito; Davies, M. Frances; Clark, J. David; Kobilka, Brian K.; Maze, Mervyn
CS Department of Functional Restoration, Stanford University, Stanford, CA, USA
SO Anesthesiology (2002), 96(2), 367-374
CODEN: ANESAV; ISSN: 0003-3022
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The authors recently established that the analgesic actions of the inhalation anesthetic nitrous oxide were mediated by noradrenergic bulbospinal neurons and spinal .**alpha.2B** adrenoceptors. They now detd. whether noradrenergic brainstem nuclei and descending spinal pathways are responsible for the antinociceptive actions of the inhalation anesthetic isoflurane, and which .alpha. adrenoceptors mediate this effect. After selective lesioning of noradrenergic nuclei by intracerebroventricular application of the mitochondrial toxin **saporin** coupled to the antibody directed against dopamine .beta. hydroxylase (D.beta.H-**saporin**), the antinociceptive action of isoflurane was detd. Antagonists for the .alpha.1 and .alpha.2 adrenoceptors were injected at spinal and supraspinal sites in intact and spinally transected rats to identify the noradrenergic pathways mediating isoflurane antinociception. Null mice for each of the three .alpha.2-adrenoceptor subtypes (.alpha.2A, .**alpha.2B**, and .**alpha.2C**) and their wild-type cohorts were tested for their antinociceptive response to isoflurane. Both D.beta.H-**saporin** treatment and chronic spinal transection enhanced the antinociceptive effects of isoflurane. The .alpha.1-adrenoceptor antagonist prazosin also enhanced isoflurane antinociception at a supraspinal site of action. The .alpha.2-adrenoceptor antagonist yohimbine inhibited isoflurane antinociception, and this effect was mediated by spinal .alpha.2 adrenoceptors. Null mice for the .alpha.2A-adrenoceptor subtype showed a reduced antinociceptive response to isoflurane. The authors suggest that, at clin. effective concns., isoflurance can modulate nociception via three different mechanisms: (1) a pronociceptive effect requiring descending spinal pathways, brainstem noradrenergic nuclei, and supraspinal .alpha.1 adrenoceptors; (2) an antinociceptive effect requiring descending noradrenergic neurons and spinal .alpha.2A adrenoceptors; and (3) an antinociceptive effect mediated

within the spinal cord for which no role for **adrenergic** mechanism has been found.

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